DANA-FARBER CANCER INSTITUTE

Conflicts of Interest

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Associate Professor of Pediatrics

Ethical and Regulatory Aspects of Clinical Research
National Institutes of Health Clinical Center
October 12, 2011

Disclosure

- I am a paid member of a Safety Monitoring Committee for Genzyme Corporation

Goals

- Understand concerns about bias related to investigators' financial ties with industry
- Consider implications of recent data regarding associations between investigators' financial ties and their scientific contributions and productivity
- Review potential policy solutions to the problem of academic-industry financial ties, along with their limitations

The Avandia Story

Year	Event
1999	Rosiglitazone (Avandia, GlaxoSmithKline) approved as mono- or combination therapy to improve glycemic control in patients with type 2 diabetes mellitus • Label includes precautions for patients with heart failure
2005	Internal GSK meta-analysis finds non-significantly increased risk of ischemic cardiovascular events
2006	FDA strengthens warning related to CV events
2007	Nissen & Wolski publish meta-analysis in NEJM showing 43% increase in risk of myocardial infarction FDA advisory committee finds increased CV risk but votes to keep drug on market FDA adds boxed warning about MI risk to label

BMJ 340:785, 2010

May 2007: The Intrigue

Date	Event
May 1	Nissen & Wolski submission
May 2	NEJM sends manuscript for peer review
May 3	Peer reviewer (& GSK consultant) Steven Haffner faxes manuscript to GSK • GSK circulates widely • in an internal memo, GSK head of research affirms Nissen & Wolski's conclusions
May 10	GSK scientists & execs visit Nissen in Cleveland • Nissen secretly tapes meeting
May 14	GSK unblinds ongoing RECORD trial (European postmarketing RCT comparing rosiglitazone to active control)
May 21	Nissen & Wolski meta-analysis published online
May 24	GSK asks steering committee for permission to unblind RECORD trial

BMJ 340:785, 2010
JAMA 303:1194, 2010

Fast Forward 2010

- Senate Finance Committee (Grassley) investigation
- FDA advisory committee meeting (July)
  - FDA review concludes that "RECORD was inadequately designed and conducted to provide any reassurance about the CV safety of rosiglitazone. [The results] suggest that rosiglitazone increases the risk for MI, although the confidence intervals…are wide and include no risk while biases in the study suggest that the true risk could be higher."
  - In divided vote, committee recommends stricter controls on prescription of rosiglitazone

Definition of COI

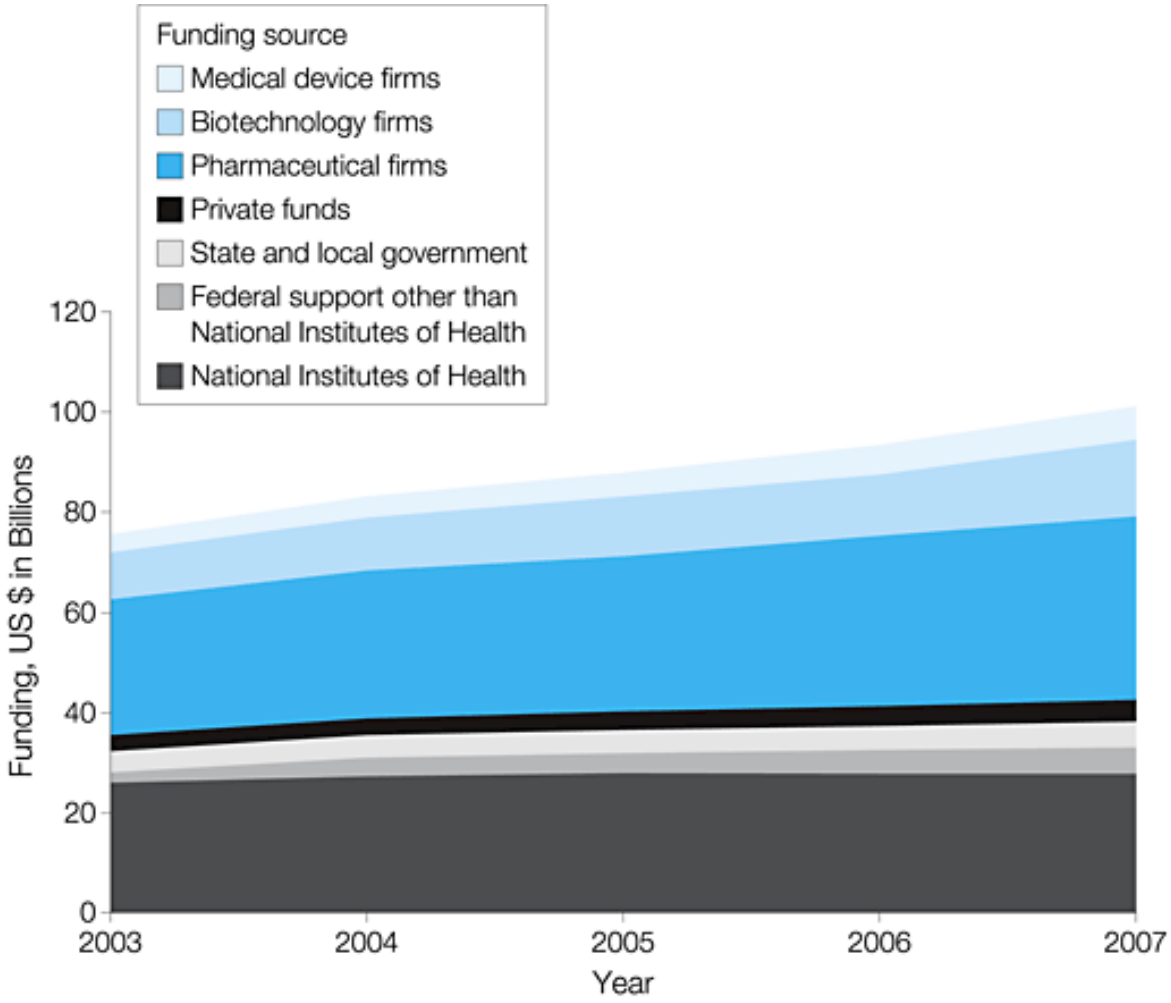
- "A COI is a set of *circumstances* that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest."

Lo, B., M. J. Field, et al. (2009). *Conflict of interest in medical research, education, and practice.* Washington, D.C., National Academies Press.

Why Do We Care About COI in Research?

- Potential to influence investigators' judgments
  - Biased science
  - Increased risks to subjects(?)
- Potential to impede scientific openness
- Potential to undermine public trust

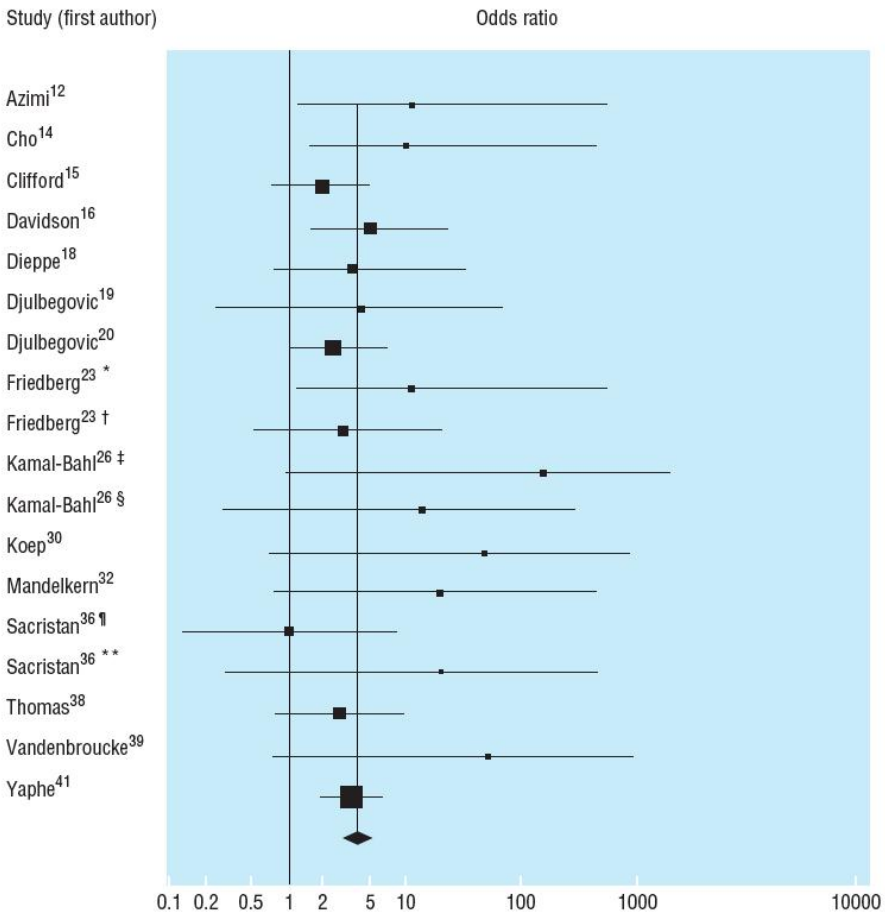
National Biomedical Research Expenditures



JAMA

JAMA 303:137, 2010

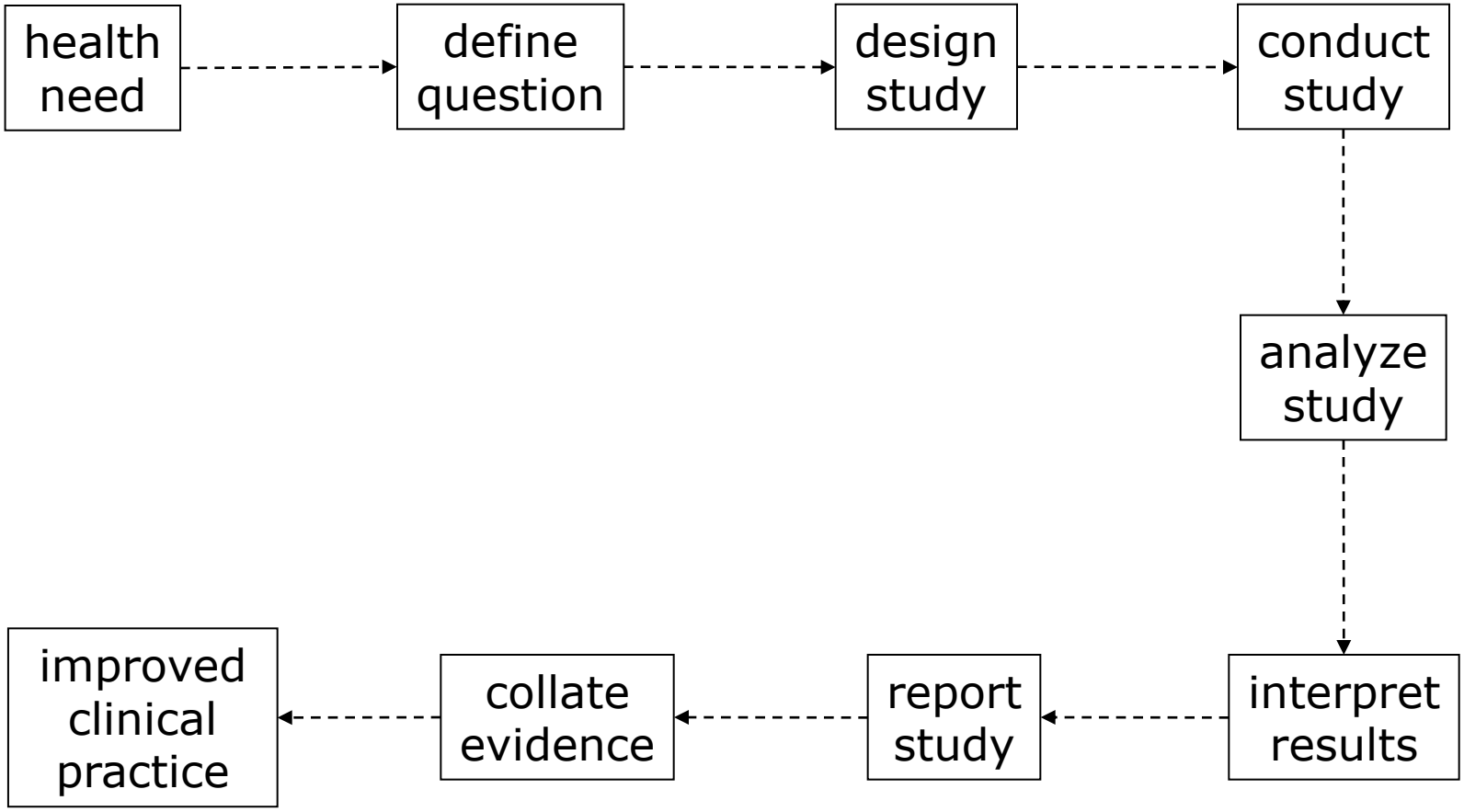
Relation Between Source of Support & Study Outcome



Summary OR 4.1 (CI 3.0-5.5)

BMJ 326:1167, 2003; see also JAMA 289:454, 2003

Mechanisms?

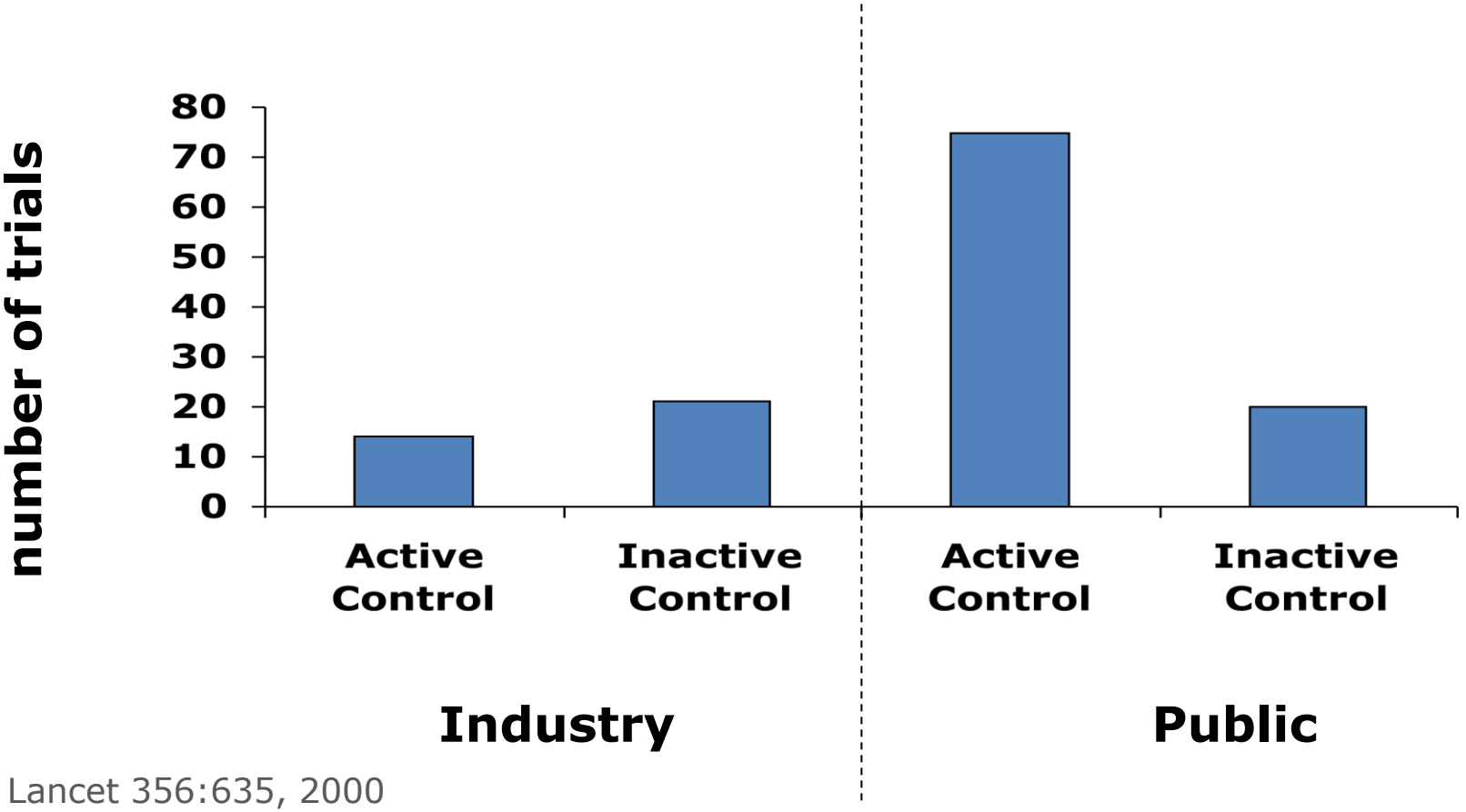

health need
define question
design study
conduct study
analyze study
interpret results
report study
collate evidence
improved clinical practice

Mechanisms

- Some hypotheses
  - Choice of control group
  - Bias in conducting studies (e.g., ascertaining events)
  - Bias in analysis
  - Bias in interpretation (“spin”)
  - Bias in publication

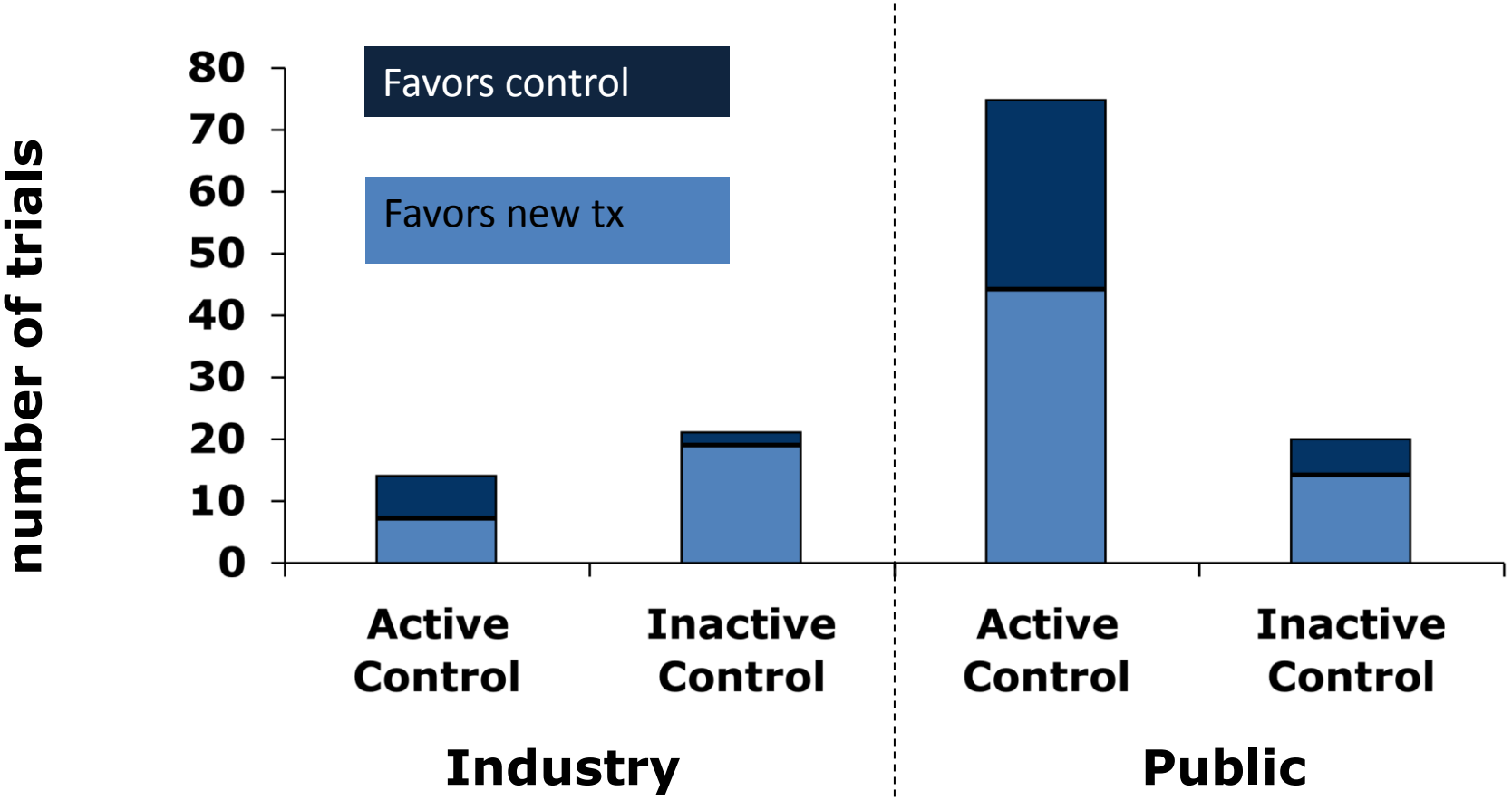
Choice of Control

- 130 randomized trials for multiple myeloma (1996-8)



Lancet 356:635, 2000

Choice of Control



Lancet 356:635, 2000

Study Conduct

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 14, 2010

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products

Subject: Cardiovascular events in RECORD, NDA 21-071/S-035

Through: Norman Stockbridge, M.D., Ph.D.
Division Director

To: Jena Weber, Project Manager
Division of Metabolism and Endocrinology Products

Table 3: Summary of Reviewed CRFs

	rosiglitazone		control	
	n	%	n	%
randomized & treated - GSK "ITT"	2220	100%	2227	100%
CRFs reviewed (total 549)	278	13%	271	12%
CRFs with problems	45	2.0%	25	1.1%
favoring rosiglitazone	44	2.0%	13	0.6%
favoring control	1	0.05%	12	0.5%
overall which arm is favored	57	10.4% of 549	13	2.4% of 549

Analysis

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use

S. Swaroop Vedula, M.D., M.P.H., Lisa Bero, Ph.D., Roberta W. Scherer, Ph.D., and Kay Dickersin, Ph.D.

- Reviewed 20 clinical trials of gabapentin for off-label indications
  - Compared outcomes of published reports to those in internal company documents
  - 12/20 trials published

Spin?

- Als-Nielsen studied relationship between funding source & conclusion in 370 drug trials included in Cochrane meta-analyses

Table 3. Estimated Effect of Funding, Treatment Effect, and Double Blinding on Conclusions

Characteristic	Odds Ratio (95% Confidence Interval)	*P* Value
Funding		.005
Nonprofit organizations	1.0	
Not reported	2.4 (0.9-6.8)	.10
Nonprofit and for-profit organization	2.6 (0.9-7.9)	.09
For-profit organizations	5.3 (2.0-14.4)	.001
Treatment effect (*z* score)*	0.6 (0.5-0.7)	<.001
Double blinding	2.9 (1.4-6.0)	.004

*The likelihood of recommending the experimental drug as the treatment of choice decreased with higher *z* scores (the higher the score the smaller the benefit of the experimental drug).

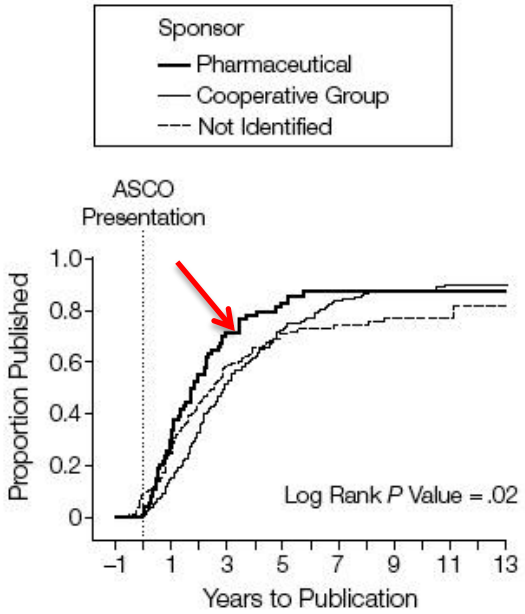
JAMA 290:921, 2003

Publication

- Krzyzanowska et al reviewed publication outcomes of 510 large RCTs presented at an oncology meeting

Figure 3. Time to Publication by Sponsorship and by Type of Result and Sponsorship

A Time to Publication by Sponsorship

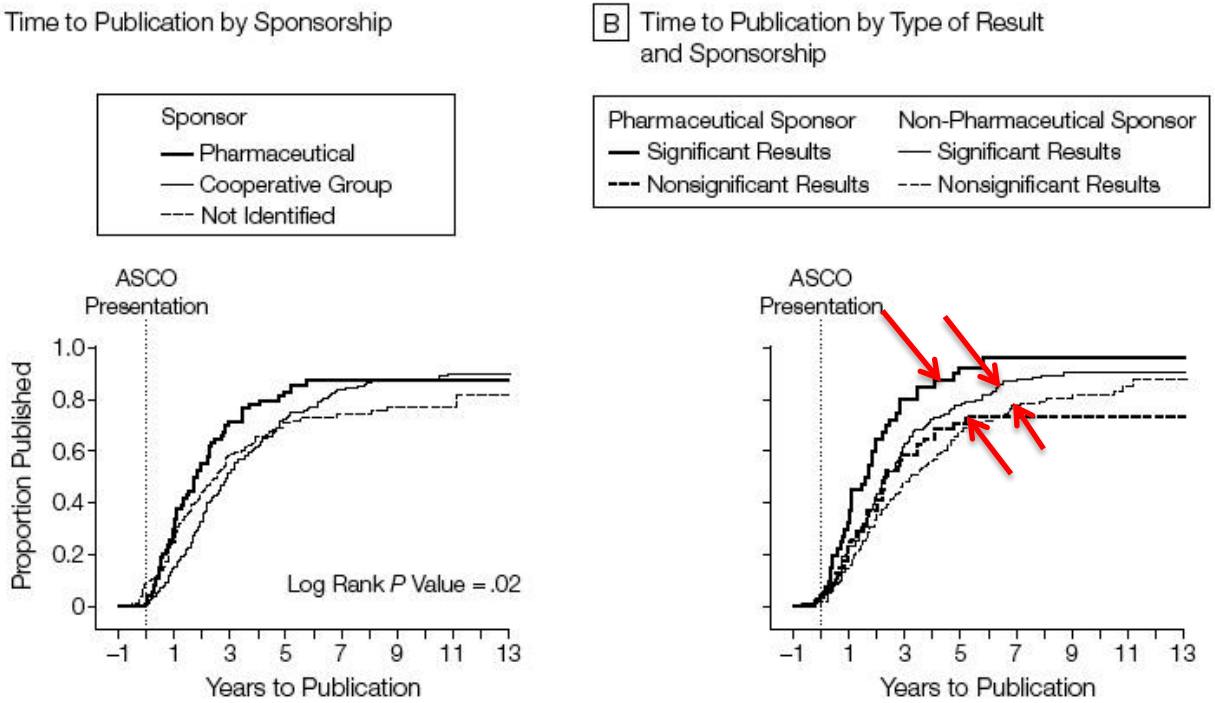


JAMA 290:495, 2003

Publication

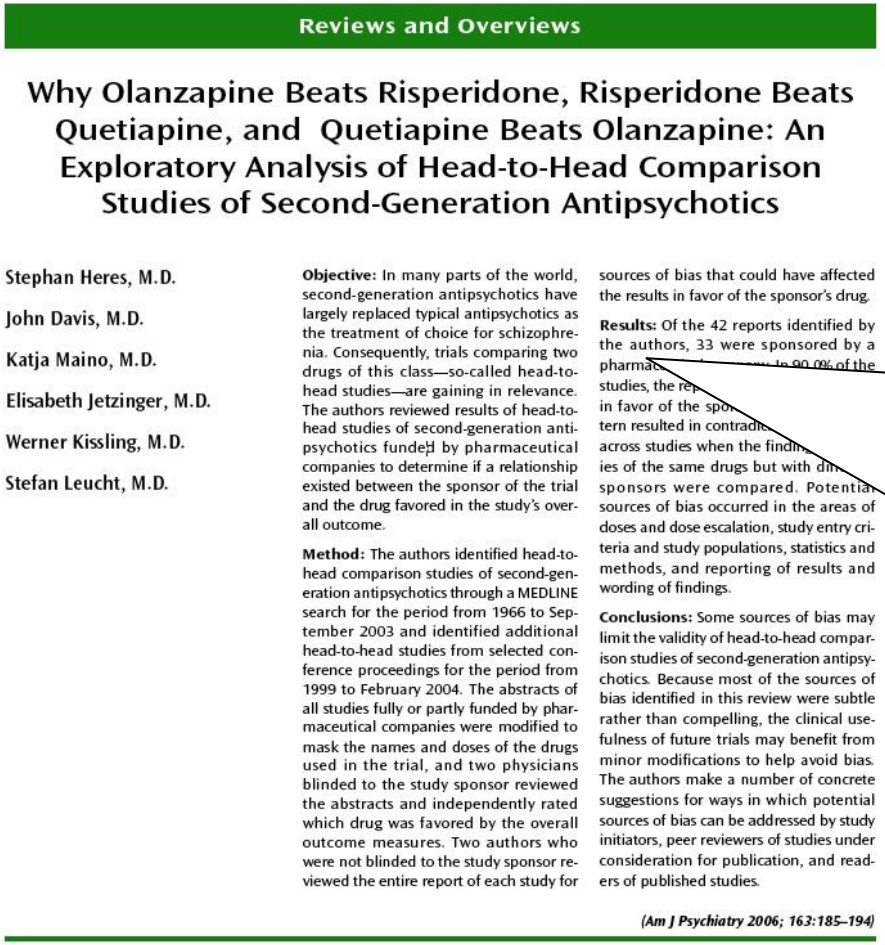
- Krzyzanowska et al reviewed publication outcomes of 510 large RCTs presented at an oncology meeting

Figure 3. Time to Publication by Sponsorship and by Type of Result and Sponsorship



JAMA 290:495, 2003

Putting It Together



Reviews and Overviews

Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

Stephan Heres, M.D.
John Davis, M.D.
Katja Maino, M.D.
Elisabeth Jetzinger, M.D.
Werner Kissling, M.D.
Stefan Leucht, M.D.

Objective: In many parts of the world, second-generation antipsychotics have largely replaced typical antipsychotics as the treatment of choice for schizophrenia. Consequently, trials comparing two drugs of this class—so-called head-to-head studies—are gaining in relevance. The authors reviewed results of head-to-head studies of second-generation antipsychotics funded by pharmaceutical companies to determine if a relationship existed between the sponsor of the trial and the drug favored in the study's overall outcome.

Method: The authors identified head-to-head comparison studies of second-generation antipsychotics through a MEDLINE search for the period from 1966 to September 2003 and identified additional head-to-head studies from selected conference proceedings for the period from 1999 to February 2004. The abstracts of all studies fully or partly funded by pharmaceutical companies were modified to mask the names and doses of the drugs used in the trial, and two physicians blinded to the study sponsor reviewed the abstracts and independently rated which drug was favored by the overall outcome measures. Two authors who were not blinded to the study sponsor reviewed the entire report of each study for sources of bias that could have affected the results in favor of the sponsor's drug.

Results: Of the 42 reports identified by the authors, 33 were sponsored by a pharmac... ...to 90.0% of the studies, the re... in favor of the spo... tern resulted in contradic... across studies when the findin... ies of the same drugs but with di... sponsors were compared. Potentia... sources of bias occurred in the areas of doses and dose escalation, study entry criteria and study populations, statistics and methods, and reporting of results and wording of findings.

Conclusions: Some sources of bias may limit the validity of head-to-head comparison studies of second-generation antipsychotics. Because most of the sources of bias identified in this review were subtle rather than compelling, the clinical usefulness of future trials may benefit from minor modifications to help avoid bias. The authors make a number of concrete suggestions for ways in which potential sources of bias can be addressed by study initiators, peer reviewers of studies under consideration for publication, and readers of published studies.

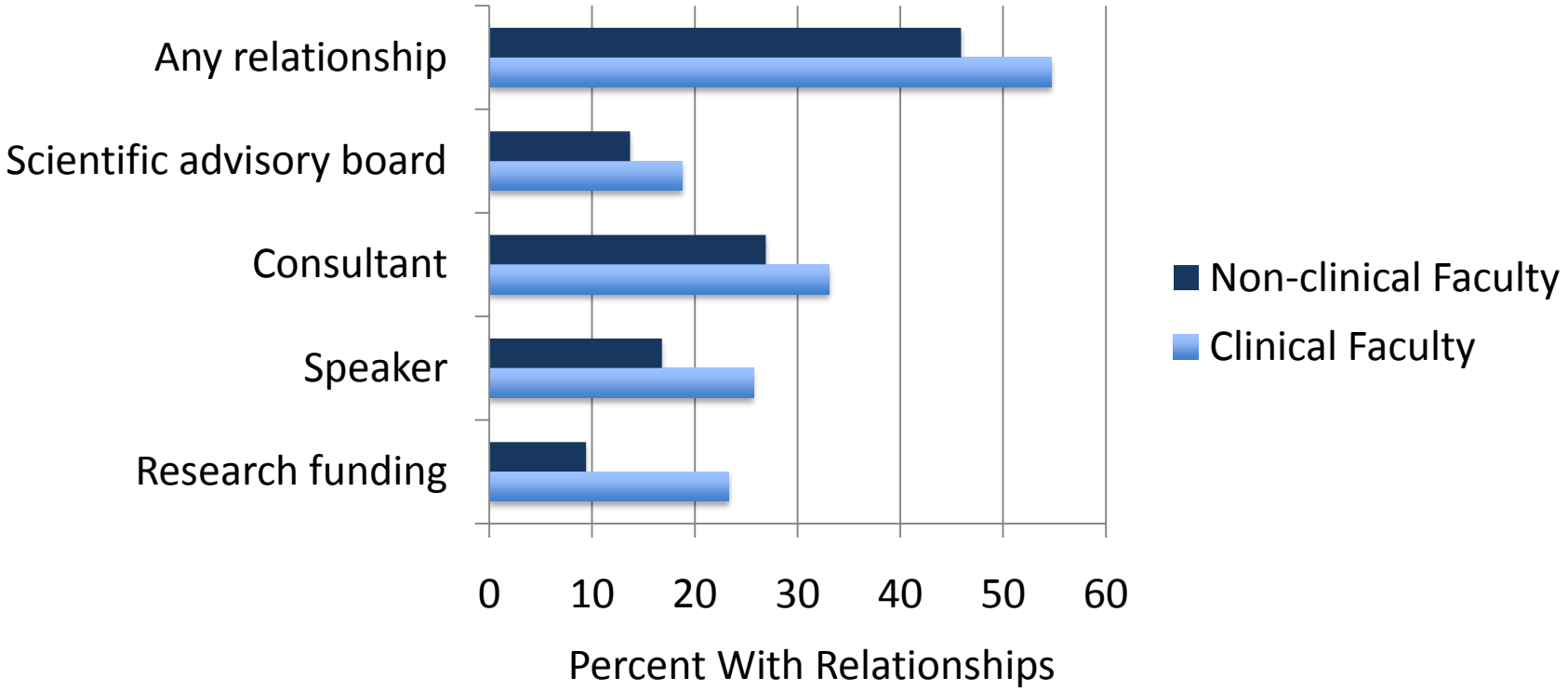
(Am J Psychiatry 2006; 163:185–194)

Results: Of the 42 reports identified by the authors, 33 were sponsored by a pharmaceutical company. In 90.0% of the studies, the reported overall outcome was in favor of the sponsor's drug. This pattern resulted in contradictory conclusions across studies when the findings of studies of the same drugs but with different sponsors were compared. Potential sources of bias occurred in the areas of doses and dose escalation, study entry criteria and study populations, statistics and methods, and reporting of results and wording of findings.

What About Personal Financial Ties?

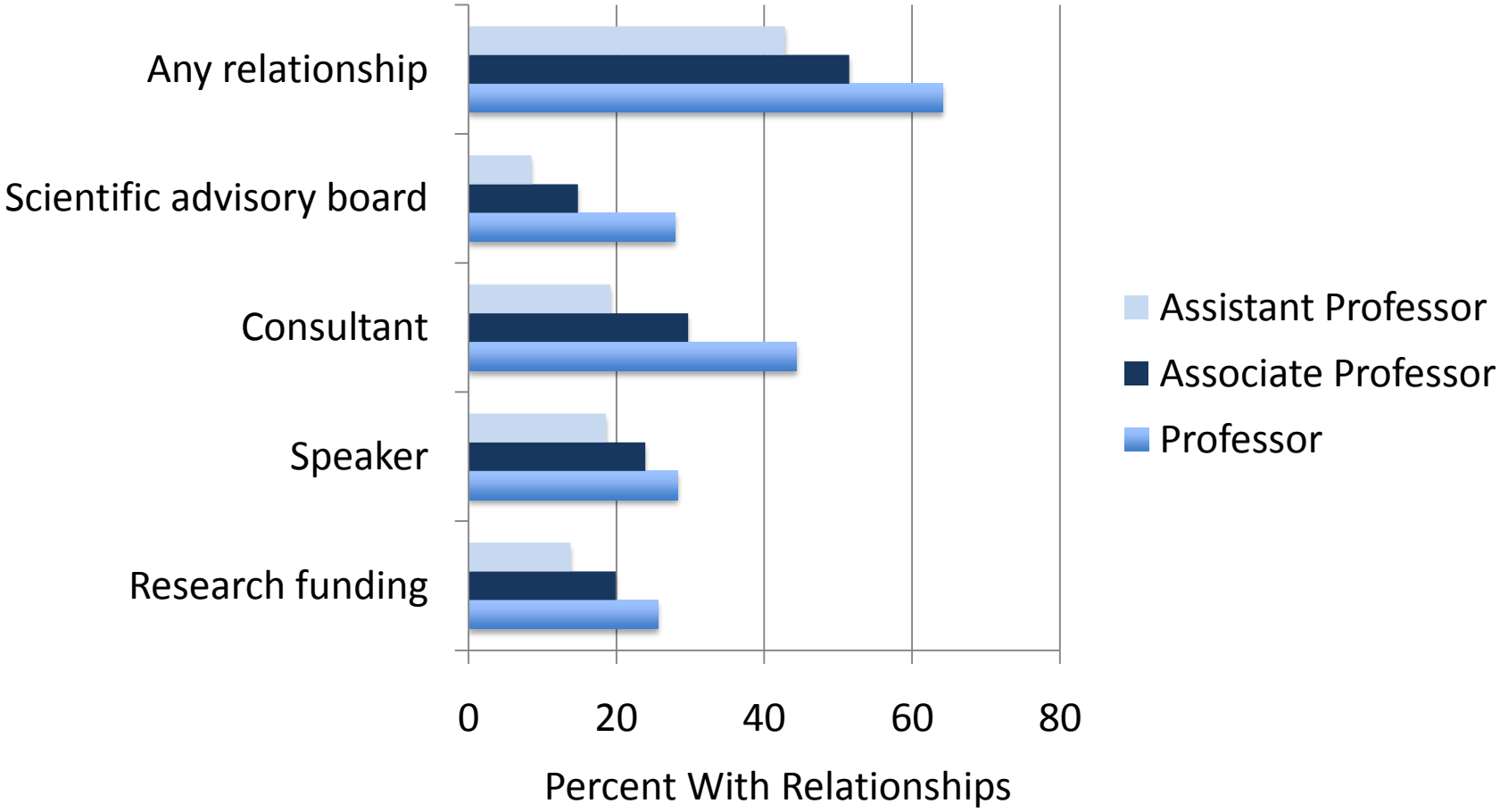
Prevalence of Personal Financial Ties

Zinner et al surveyed a stratified random sample of life-sciences faculty at the 50 U.S. universities with the most NIH support



Health Affairs 28:1814, 2009

Prevalence of Personal Financial Ties, by Academic Rank



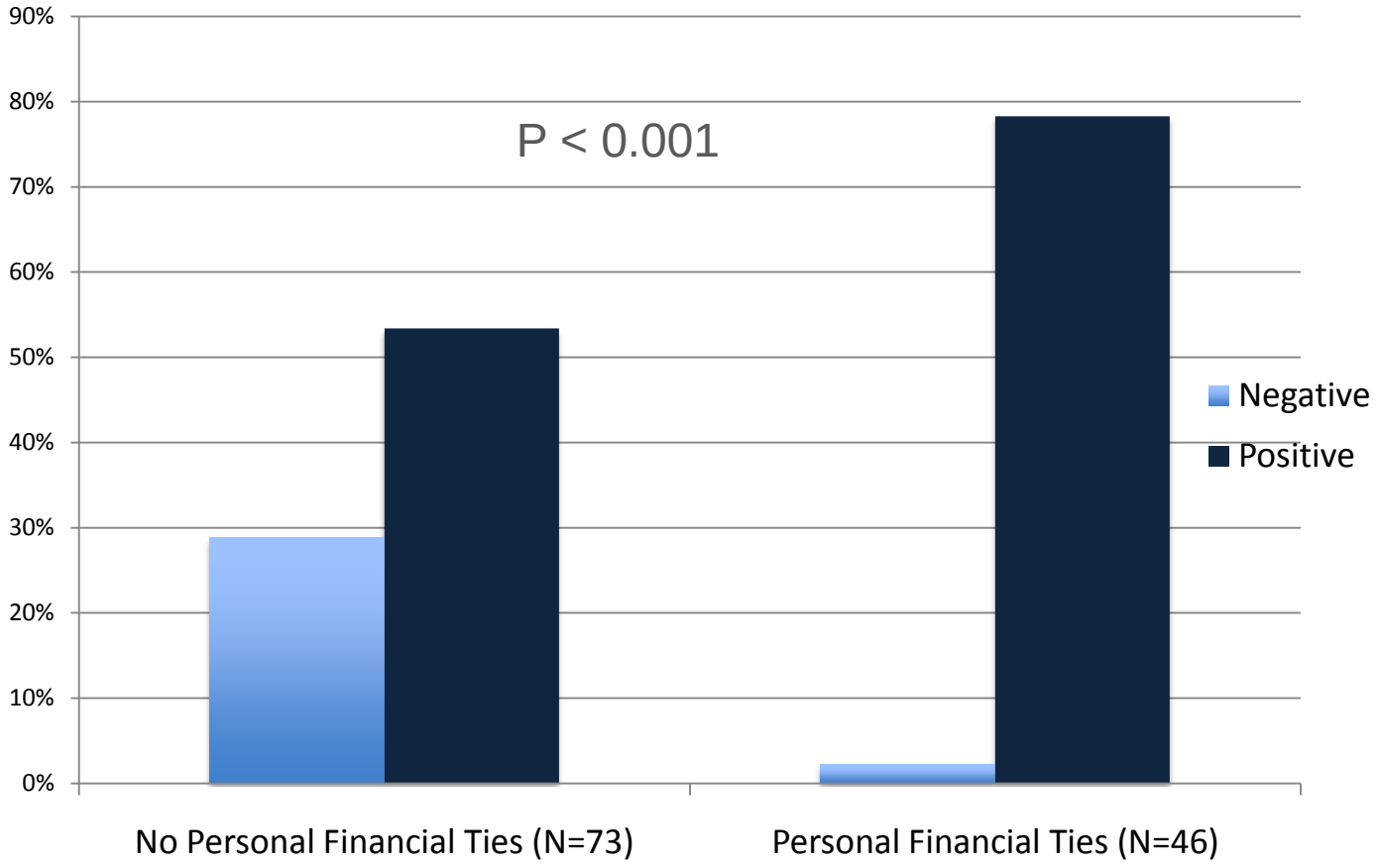
Health Affairs 28:1814, 2009

Outcomes among Drug Trials, by Presence or Absence of Personal Financial Ties

- Few data
- Friedman & Richter reviewed all original reports published in NEJM or JAMA in 2001
  - 16-22% of articles (N=398) had at least one author who reported a personal financial tie to industry

JGIM 19:51, 2004; see also Am J Psychiatry 2005;162:1957

Outcomes among Drug Trials, by Presence or Absence of Personal Financial Ties



*analysis does not control for source of study funding

JGIM 19:51, 2004

Back to Avandia

- Wang et al reviewed articles that commented on rosiglitazone and the risk of MI
  - 108/202 articles included a COI statement
  - 90 authors (45%) reported a financial COI

BMJ 340:1344, 2010

Relationship Between Financial Ties & Authors' Positions on Avandia's MI Risk

BMJ 340:1344, 2010

Goals

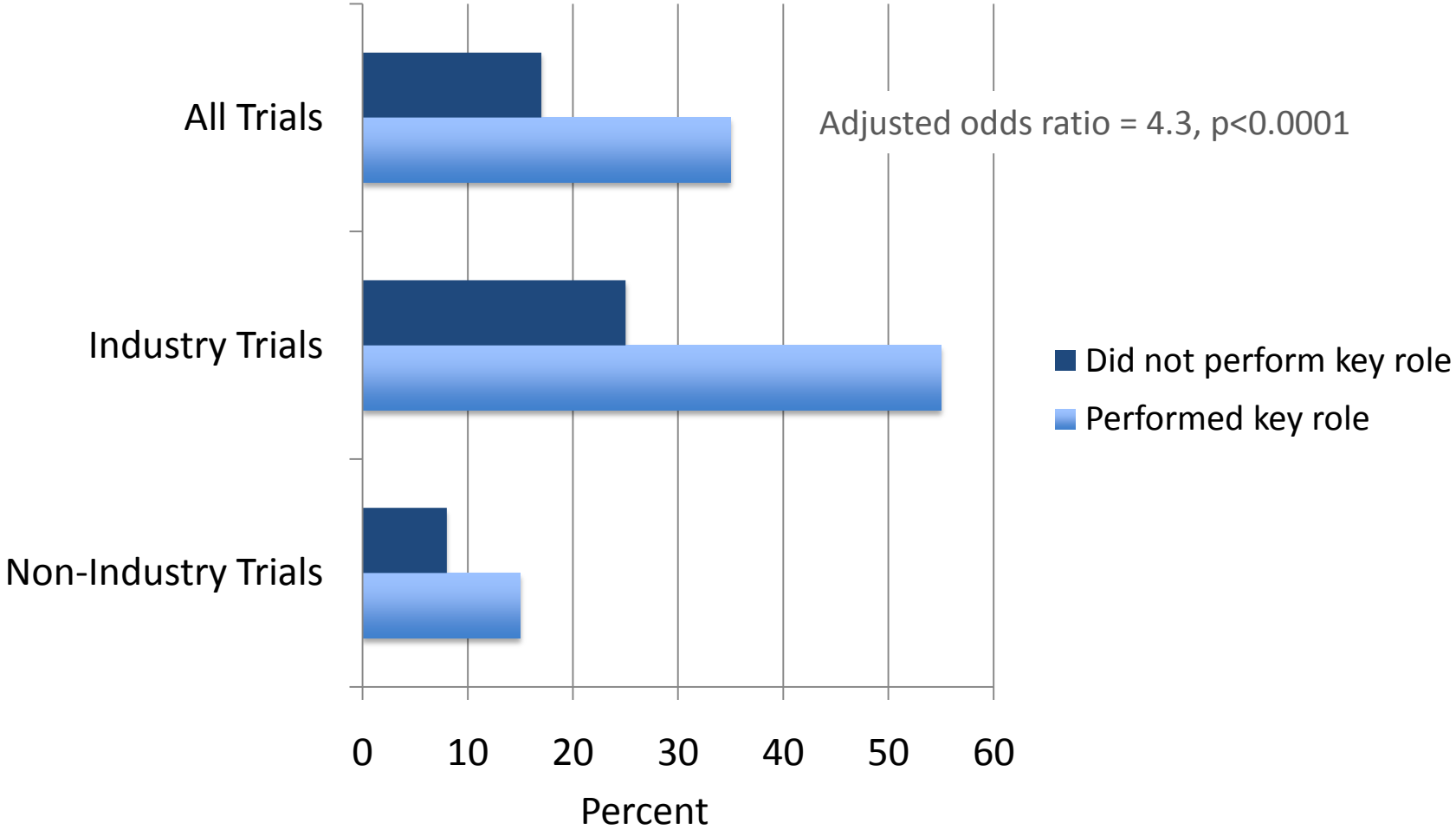
- ✓ Understand concerns about bias related to investigators' financial ties with industry
- Consider implications of recent data regarding associations between investigators' financial ties and their scientific contributions
- Review potential policy solutions to the problem of academic-industry financial ties, along with their limitations

Who Has Financial Ties?

- We identified all reports of clinical trials of drugs or biologics published in the *Journal of Clinical Oncology* between January 2006 & June 2007 (N=235)
  - We abstracted financial disclosures and authorship contributions of all authors (N=2927)
  - We asked whether authors who reported performing key scientific roles (conception & design, analysis & interpretation, or drafting of manuscript) were more likely than other authors to report financial ties

J Clin Oncol 28:1316, 2010

Percent of Authors Reporting Financial Ties, by Sponsorship and Performance of Key Role



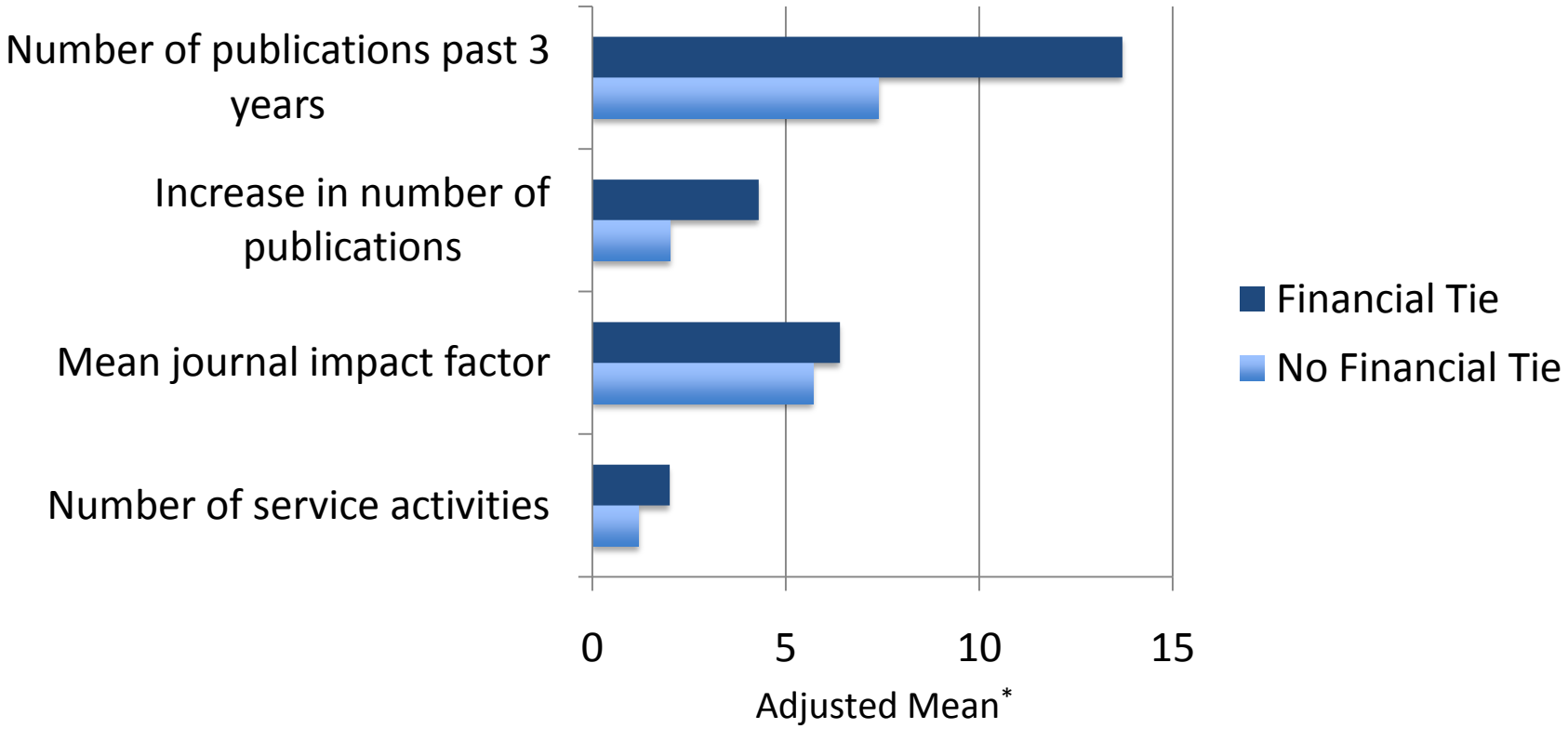
J Clin Oncol 28:1316, 2010

How Are Financial Ties Related to Academic Productivity?

- Recall Zinner et al survey of a stratified random sample of life-sciences faculty at the 50 U.S. universities with the most NIH support

Health Affairs 28:1814, 2009

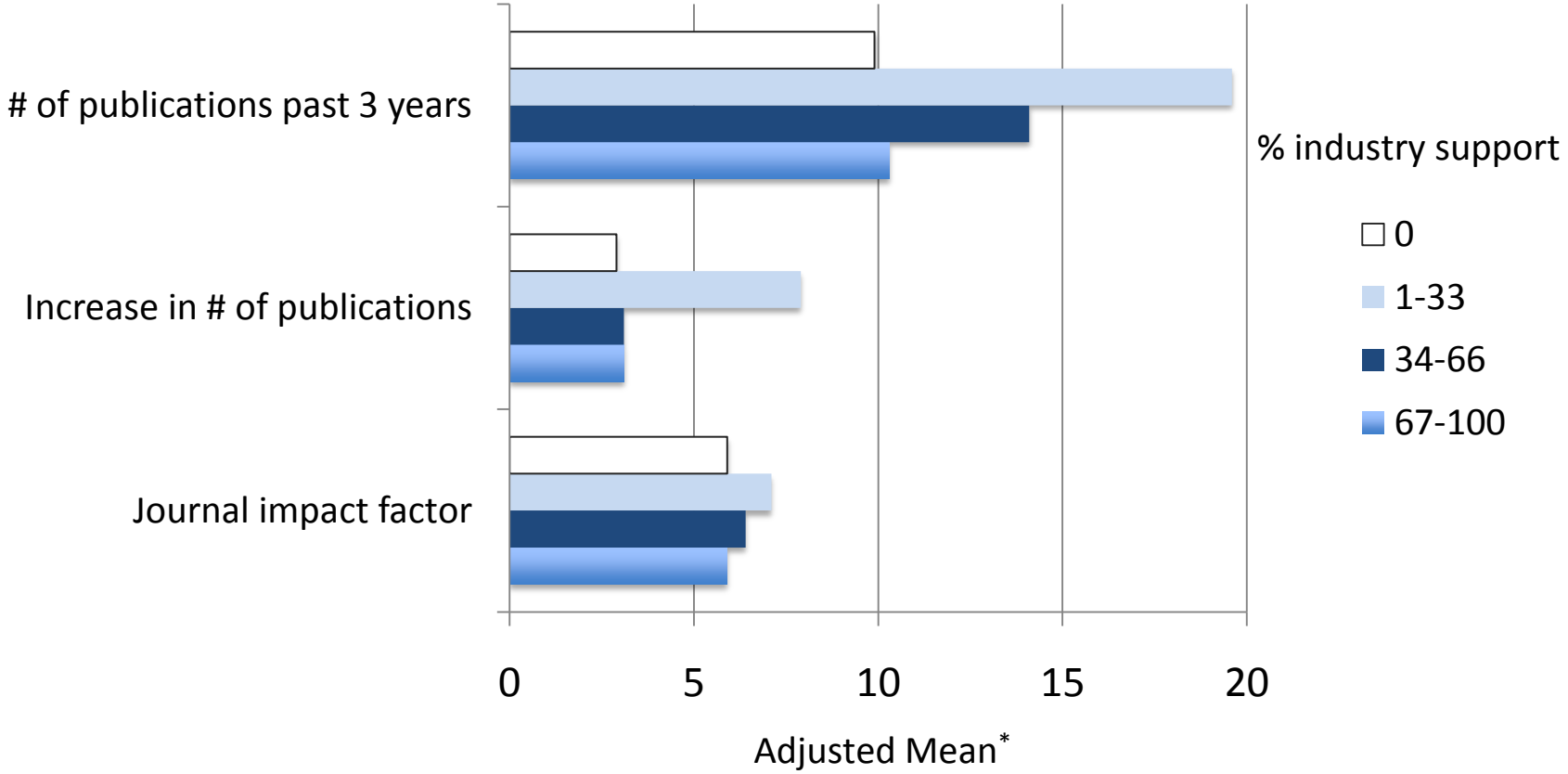
Relationship Between Financial Ties and Academic Productivity



*Adjusted for rank, years in profession, sex, total research funding, clinical department

Health Affairs 28:1814, 2009

Academic Productivity vs. Percent of Research Budget Supported by Industry



*Adjusted for rank, years in profession, sex, total research funding, clinical department

Health Affairs 28:1814, 2009

Implications of Recent Data

- Academic authors with financial ties make greater scientific contributions than their peers without ties
- Industry support, at least within a balanced research portfolio, correlates with greater scientific productivity
- Mechanisms behind these relationships are unknown
- Unclear how increased restrictions on academic-industry collaboration might affect scientific output and translation

Goals

- ✓ Understand concerns about bias related to investigators' financial ties with industry
- ✓ Consider implications of recent data regarding associations between investigators' financial ties and their scientific contributions
- Review potential policy solutions to the problem of academic-industry financial ties, along with their limitations

Policy Context

- Much attention
  - Congress
  - State legislatures (MN, ME, MA, WV, VT)
  - Federal funders
  - Universities, academic medical centers, & their representative organizations
  - Institute of Medicine
  - Company & trade association policies
  - Journals

Strategies For Addressing Financial COI

- Disclose
- Manage
- Prohibit

Disclosure

- To whom?
  - Sponsors?
  - IRBs?
  - Institutions/COI committees?
  - Journals, readers, meeting attendees?
  - Research subjects?

Recipients' Views on Disclosure

REVIEW ARTICLE

HEALTH CARE REFORM

The Impact of Disclosing Financial Ties in Research and Clinical Care

A Systematic Review

Adam Licurse, BA; Emma Barber, BS; Steve Joffe, MD; Cary Gross, MD

Background: Despite increased demand for disclosure of physician and researcher financial ties (FTs) to industry, little is known about patients', research participants', or journal readers' attitudes toward FTs.

Methods: We systematically reviewed original, quantitative studies of patients', research participants', or journal readers' views about FTs to pharmaceutical and medical device companies. The MEDLINE, Scopus, and Web of Knowledge databases were searched for English-language studies containing original, quantitative data on attitudes toward FTs. We screened 6561 citations and retrieved 244 potentially eligible abstracts. Of these, 20 met inclusion criteria.

Results: Eleven studies assessed FTs and perceptions of quality. In clinical care, patients believed FTs decreased the quality and increased the cost of care. In research, FTs affected perceptions of study quality. In 2 studies, readers' perceptions of journal article quality [illegible] after disclosure of FTs. Eight studies assess[illegible]ceptability of FTs. Patients were more likel[illegible]ew personal gifts to physicians as unacceptabl[illegible]pared with professional gifts. In 6 of the 10 studi[illegible]at assessed the importance of disclosure, most pati[illegible]s and research participants believed FTs should be disclosed; in the other 4, approximately one-quarter believed FTs should be disclosed. Among the 7 studies assessing willingness to participate in research, approximately one-quarter of participants reported less willingness after disclosure of FTs.

Conclusions: Patients believe that FTs influence professional behavior and should be disclosed. Patients, physicians, and research participants believe FTs decrease the quality of research evidence, and, for some, knowledge of FTs would affect willingness to participate in research.

Arch Intern Med. 2010;170(8):675-682

In 6 of the 10 studies that assessed the importance of disclosure, most patients and research participants believed FTs should be disclosed; in the other 4, approximately one-quarter believed FTs should be disclosed. Among the 7 studies assessing willingness to participate in research, approximately one-quarter of participants reported less willingness after disclosure of FTs.

Health Care Reform & Disclosure

- Federal health care reform includes provisions of Physician Payments Sunshine Act
  - US manufacturers of drugs, devices, biologics, and medical supplies covered under Medicare, Medicaid, or SCHIP must report payments to *physicians and teaching hospitals* to DHHS on an annual basis
  - Covers all types of payments worth $10 or more, including research funding
  - Implementation begins January 1, 2012
  - Substantial fines for noncompliance, esp. if knowing

http://www.prescriptionproject.org/tools/initiatives_factsheets/files/Sunshine-fact-sheet-3.23.10.pdf

Management

- Examples from U. of Washington *Significant Financial Interest Disclosure Policy*
  - Monitoring of research by independent co-researchers and/or reviewers, disinterested individuals or committees
  - Placing copies of research data with a neutral party
  - Annual reporting to the University

http://uwmedicine.washington.edu/Global/policies/Pages/Conflict-of-Interest-with-Commercial-or-Non-Profit-Entities.aspx

New NIH Rules for Extramural Grantees

- Changes definition of Significant Financial Interest (SFI) from $10000 to $5000
- Requires that all SFI be disclosed to institution
  - Institution then determines which SFI constitute COI
  - Institution must develop management plans for all identified financial COI
  - Institution must disclose nature of COI and key elements of management plan to PHS funder
  - Institution must post COI information on public website, or make available on written request within 5 business days

http://grants.nih.gov/grants/policy/coi/

Prohibition

- Institute of Medicine
  - "Academic medical centers and other research institutions should establish a policy that individuals generally may not conduct research with human participants if they have a significant financial interest in an existing or potential product or a company that could be affected by the outcome of the research. Exceptions to the policy should be made public and should be permitted only if the conflict of interest committee (a) determines that an individual's participation is essential for the conduct of the research and (b) establishes an effective mechanism for managing the conflict and protecting the integrity of the research."

Lo, B., M. J. Field, et al. (2009). *Conflict of interest in medical research, education, and practice.* Washington, D.C., National Academies Press.

How Well Do These Rules Accomplish Their Goals?

- Minimize risks to human subjects?
- Reduce risk of bias in science?
  - vs. reduce involvement of faculty, academic institutions, & noncommercial funders in biased science
- Protect the reputations of academic faculty and institutions?
  - Protect “academic values”
- Preserve public trust in research?

Summary

- Strong evidence base for bias in industry-funded research
- Weaker, but growing, evidence base that personal financial ties pose additional risk
- New evidence that financial ties correlate with scientific contributions & productivity
- Much policy activity, but unclear how well policies accomplish key goals